Commissioning support document for the primary care use of

**PreventID® CalScreen®**
(Calprotectin)

**Executive Summary**

- PreventID® CalScreen® is a new, simple, rapid, point-of-care test to determine whether patients presenting undiagnosed chronic abdominal symptoms have above-normal levels of faecal calprotectin – a marker of inflammatory activity in the bowel that may be associated with disorders such as inflammatory bowel disease (IBD) or bowel cancer.

- It is estimated that over 30% of patients who are referred for diagnostic endoscopy have functional bowel disorders such as irritable bowel syndrome (IBS) and that these patients’ referrals could have been avoided.

- The cost of these avoidable referrals is in excess of £130 million per year (about £600 thousand per Clinical Commissioning Group (CCG) annually).

- Calprotectin is recommended as a screening tool in Primary Care by the British Society of Gastroenterology and the National Institute for Health and Care Excellence (NICE), where it is recommended as ‘an option to support clinicians with the differential diagnosis of IBD or IBS’.

- Current NICE IBS guidelines offer clear and simple guidance on what questions to ask and when to refer.

- PreventID® CalScreen® is a semi-quantitative, immunochromatographic rapid test for the detection of calprotectin in faeces. The use of this test with a cut-off at 50 μg/g calprotectin enables the rapid screening of patients with chronic abdominal symptoms and the differentiation between inflammatory (i.e. organic disease >50 μg/g) and non-inflammatory (i.e. functional disease <50 μg/g) conditions.

- The test takes up to 10 minutes to conduct.

- It is a highly accurate test which has been validated against the PhiCal Calprotectin ELISA test used in hospital pathology laboratories. This ELISA test and PreventID® CalScreen® has demonstrated the following results:
  - Sensitivity: 91.0%
  - Specificity: 94.7%

- PreventID® CalScreen® is available at a standard cost per test of £12.50 which compares favourably with the standard cost for other calprotectin point-of-care and secondary care tests of £25 in many areas.
Introduction

The purpose of this document is to present the rationale for including PreventID® CalScreen® as part of the cost-effective screening and diagnosis of patients with chronic abdominal symptoms.

Over half a million patients are referred to hospital for endoscopies and, of them, 32% are found to have IBS. Based on Ferring’s Budget Impact Model, the total cost of scoping these patients is in excess of £130 million per year – over £1 million per Clinical Commissioning Group or Health Board in the UK.

This document will aim to show how these avoidable costs can be allayed with the use of a simple, rapid and non-invasive point-of-care test.

Chronic Abdominal Symptoms

Over 20% of the population will present to Primary Care suffering from undiagnosed chronic abdominal symptoms.

Based on the average prevalence in the UK the conditions that could present include:

- Irritable bowel syndrome (20,000 per 100,000 population)
- Coeliac disease (1,000 per 100,000 population)
- Inflammatory bowel disease (IBD) – Crohn’s disease or ulcerative colitis (400 per 100,000 population)
- Colorectal cancer (41.3 per 100,000 population)

The majority of patients will consult complaining of abdominal pain, bloating and altered bowel habit. Very often, their symptoms will be distressing to them and the problem for General Practitioners has been to have a reliable test that will distinguish between functional disorders – such as chronic idiopathic constipation (CIC) or IBS – which can be treated effectively in the GP’s surgery and organic disease – such as IBD or cancer – that requires referral for specialist follow-up.

IBD, IBS and CIC are all associated with significant co-morbidity, much of which can have substantial impact on the general economy in terms of reduced time at work and unwillingness to take part in social occasions. IBD is associated with a wide range of disorders including hepatic, GI, obesity, cardiovascular and psychiatric. For example, IBD patients had an incidence of venous thromboembolisms (VTEs) with a Hazard Ratio of 3.4 compared to the normal population.

IBS sufferers have more days off work than non-sufferers with 3.9 days in bed (non-sufferers had 2.7 days); 5.5 days sick off work (versus 3.1 days); 8.4 days seeing a doctor or nurse (versus 5.2 days); 10.2 days when work activities had to be cut short (versus 4.8 days).

Therefore it can be concluded that the costs associated with a delayed diagnosis of ‘chronic abdominal symptoms’ represent an increased expenditure on primary care time and referrals to secondary care, significantly more co-morbidities (which themselves have cost implications), very real economic costs due to lost work time and reduced social activity.

It can be further concluded that a process whereby patients with suspected IBS or CIC (who will make up the majority of consultations) can have rapid access to treatment will mitigate some of these costs – especially when it comes to avoidable endoscopy. For that to happen, GPs will need access to an easy-to-use diagnostic tool which will give them a reliable guide as to which patients need to be referred for further investigation and which can be treated with confidence in primary care.
The diagnostic tool that is gaining acceptance among GI specialists most rapidly at present is calprotectin. Measurement of faecal calprotectin is a biochemical test for inflammatory activity in the bowel. It replaces the need for invasive colonoscopy or radio-labelled white cell scanning in many clinical scenarios.

Calprotectin is a 36kDa calcium and zinc binding protein which accounts for more than 60% of neutrophils’ cytosolic proteins. In vitro studies show it has bacteriostatic and fungistatic properties. It is resistant to enzymatic degradation and can be easily measure in faeces.10

The main diseases that cause an increased excretion of faecal calprotectin are Crohn’s disease, ulcerative colitis and neoplasms (cancer). In addition, infection can raise levels of calprotectin. Crucially, levels of faecal calprotectin are normal in patients with IBS.11,12

Although a relatively new test, faecal calprotectin is regularly used as an indicator for IBD during treatment and as diagnostic marker. PreventID® CalScreen® classifies normal levels of faecal calprotectin at below 50μg/g, therefore levels detected above that in primary care should be considered for secondary care referral and further investigation using endoscopy.

Determination of calprotectin can be used for:
1. Identifying organic bowel disease versus functional bowel disease (IBS), and thus avoiding the need for invasive tests such as colonoscopy
2. Assessing efficacy of IBD treatments
3. Predicting relapses or flares of IBD
4. Offering an alternate diagnostic test for patients who are scared of needles or endoscopy

Calprotectin (including PreventID® CalScreen) has been reviewed by the National Institute for Health and Care Excellence (NICE) and has been recommended as an option to support clinicians with the differential diagnosis of IBS and IBD in adults with recent onset of lower gastrointestinal symptoms for whom specialist assessment is being considered if:

- Cancer is not suspected having considered the risk factors,
  and
- appropriate quality assurance processes and locally agreed care pathways are in place13

Also, recommendations for its use have been issued by the British Society of Gastroenterology (BSG). The BSG says that faecal calprotectin tests should be more widely used: 14

- By GPs to help them refer suspected IBD patients for investigation
- In monitoring current medical therapies avoiding need for colonoscopy
- Specifically in monitoring biologic therapies to assess continuation of therapy or possible trial withdrawal

Actual experience of calprotectin in primary care has been reported in 2013 by the NHS Technology Adoption Centre (NTAC).15 The conclusion of the report was that the implementation of calprotectin testing was felt by GPs and patients to have been successful. The data collected during the project showed calprotectin testing to:

- Provide additional reassurance for patients who may have anxiety or uncertainty about IBS or IBD
- Reduce the number of referrals from negative tests
- Have identified cases for referral that may not previously have been clinically indicated
- Provided greater confidence in diagnosing IBS within primary care without the need for endoscopy
Calprotectin should not be used without taking a history of the patient’s symptoms and the current NICE guidelines on IBS offer clear and simple guidance on what questions to ask and when to refer. The use of a calprotectin diagnostic test in primary care, in place of ESR and CRP, as part of the pre-referral workup of patients with undiagnosed chronic abdominal symptoms, can be incorporated into a modified diagnostic algorithm based on the NICE guidelines for IBS (Fig.1):

### Diagnostic Algorithm

Chronic abdominal symptoms >6 months (Pain, bloating, change in bowel habits)  
**Yes**

Red flag?  
- Unintentional/unexplained weight loss  
- Rectal bleeding  
- Family history of bowel/ovarian cancer  
- Change in bowel habit - looser & more frequent stools >6 weeks (>60 years)  
- Abdominal or rectal mass  
**Yes** Refer

**No**

**Yes**

IBS screening - NICE criteria  
- Abdominal pain/discomfort relieved by defaecation  
**Yes** Refer

or / and  
- Altered bowel frequency or stool form  
**No** Possibly Refer

**Yes**

IBS screening - NICE criteria: At least 2/4 symptoms  
- Altered stool passage (straining, urgency, incomplete evacuation)  
- Abdominal bloating (more common in women), distension, tension or hardness  
- Symptoms made worse by eating  
- Passage of mucus  
**Yes** Refer

**No** Possibly Refer

**Yes**

Diagnotic tests  
- Full blood count (FBC): Normal  
- Faecal calprotectin (FCP): Normal (ESR & CRP replaced by FCP)  
- Antibody testing for coeliac disease: Negative  
**No** Refer

**Yes**

High possibility of functional intestinal disease (e.g. IBS)
The Product

PreventID® CalScreen® is a semi-quantitative, immunochromatographic rapid test for the detection of calprotectin in faeces. The use of this test with a cut-off at 50 μg/g calprotectin enables the rapid screening of patients with chronic diarrhoea and the differentiation between inflammatory (i.e. organic disease >50 μg/g) and non-inflammatory (i.e. functional disease <50 μg/g) conditions.

The test device is composed of a sample well and a result window. In the result window one or two coloured lines can be seen after the test has been performed. One PreventID® CalScreen® test kit contains the following items to perform the test:

1. PreventID® CalScreen® test device (with drying agent, not required for test)
2. Sample collection device with extraction buffer solution and sample collection stick
3. Instruction sheet for sample collection

Specimen Collection

1. The faecal sample needs to be collected by the patient and it is suggested that the test is run by a healthcare professional
2. First, the cap of the sample collection device should be unscrewed and the attached sample collection stick should be introduced into the sample in one go at three different sites. Only the amount of stool that sticks to the grooves of the sample collection stick should be transferred to the sample collection device
3. The sample collection stick should then be inserted with the adhering faecal sample only once into the sample collection device which contains an extraction buffer solution. Please note: A repeated transfer of stool into the sample collection device compromises the test performance!
4. The cap must be screwed on firmly and the tube shaken well. The defined stool sample solution is then ready to use for the test
5. If PreventID® CalScreen® rapid test is not run within one day of sample collection, the sample collection device should be stored at 2-8°C, but no longer than 7 days

Test Procedure

1. The test device should be removed from the pouch and placed on a flat, dry surface. The round sample opening at the one end of the test device should be at the right side (Fig. 2). The device should be labelled with the patient’s name or identification number. Use test device immediately.

![Figure 2: PreventID® CalScreen® Test Device](image)

2. After the sample collection procedure has been completed, break off the tip of the sample collection device carefully (avoid dripping). Squeeze 3 drops of the extracted sample into the sample opening on the right side of the test device (by gently pressing the sample tube of the middle).
3. In a properly working test, a violet band will pass through the square result window in the middle of the test device.
4. The result should be interpreted 10 minutes after the last drop has been placed.
Interpreting the Test Result

A solitary red control band (C) in the result window indicates that the test has run correctly. Depending on the Calprotectin concentration, a test band (T) will appear to the right of the control band (see Figure 3 below):

![Figure 3: Interpreting the Test Results](image)

Specificity and Sensitivity of PreventID® CalScreen®

The PreventID® CalScreen® test has been validated against the PhiCal Calprotectin ELISA test. All CalScreen results in the 30 patients studied, matched the ELISA which has been established in a number of studies. Comparisons with ELISA tests using calprotectin have demonstrated the following:

- Sensitivity: 91.0%
- Specificity: 94.7%

The high results in these two parameters – which were better than those seen with lactoferrin, PNM-Elastase and polyclonal-based calprotectin assays – means that PreventID® CalScreen® would be a useful addition to the diagnostic armamentarium in patients with chronic diarrhoea and abdominal pain.

Price per Test

PreventID® CalScreen® is offered to CCGs at a price of £12.50 per test exclusive of VAT. This compares favourably with the cost of other calprotectin tests in secondary care of £25 in many areas.
The use of PreventID® CalScreen® tests as part of an assessment of patients presenting to Primary Care with chronic abdominal symptoms can result in significant savings through reductions in referral for diagnostic endoscopy.

Hospital Event Statistics (HES) data reports that there were 341,159 diagnostic endoscopic examinations of the colon (HES code H22) and 219,905 diagnostic endoscopic examinations of the lower bowel using fibreoptic sigmoidoscopes (HES code H25) in 2012. These each cost an estimated £742 including the cost of the first appointment. This estimate was based on a weighted average of the NHS reference cost for outpatient and day cases without biopsy (procedures payment by results code FZ51Z/FZ54Z), or with biopsy (procedures payment by results code FZ52Z/FZ55Z) for colonoscopy or, when used, sigmoidoscopy. The cost included an outpatient gastroenterology appointment (£164) and costs of adverse effects (an average of £12 per colonoscopy).

Of these half a million scopes, it was estimated that 32% were conducted on patients with functional bowel disorders such as IBS. These patients could therefore have avoided undergoing this invasive procedure had they been screened in primary care before referral.

The total cost of these avoidable examinations is therefore estimated at £133 million in 2012.

This represents an average saving per CCG of over £600 thousand. The cost savings for the whole of England are given in the table below together with the potential savings over a period of five years:

<table>
<thead>
<tr>
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<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
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<tbody>
<tr>
<td>Total no of diagnostic endoscopies annually (growth)</td>
<td>2%</td>
<td>561,064</td>
<td>572,285</td>
<td>583,731</td>
<td>595,406</td>
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<td>Number of diagnostic endoscopies on IBS patients</td>
<td>32%</td>
<td>179,540</td>
<td>183,131</td>
<td>186,794</td>
<td>190,530</td>
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<td>Cost of diagnostic endoscopy and 2nd care appointment</td>
<td>£741.68</td>
<td>£741.68</td>
<td>£741.68</td>
<td>£741.68</td>
<td>£741.68</td>
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<tr>
<td>Total costs of scoping IBS patients</td>
<td>£133,161,583</td>
<td>£135,824,815</td>
<td>£138,541,311</td>
<td>£141,312,137</td>
<td>£144,138,380</td>
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<tr>
<td>Cost of CalScreen test</td>
<td>£12.50</td>
<td>£12.50</td>
<td>£12.50</td>
<td>£12.50</td>
<td>£12.50</td>
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<td>Number of patients with Abdominal Symptoms seen annually</td>
<td>1,600,000</td>
<td>1,632,000</td>
<td>1,664,640</td>
<td>1,697,933</td>
<td>1,731,891</td>
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<td>Percentage tested by GPs</td>
<td>43%</td>
<td>688,000</td>
<td>701,760</td>
<td>715,795</td>
<td>730,111</td>
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<td>Costs of testing</td>
<td>£8,600,000</td>
<td>£8,772,000</td>
<td>£8,947,440</td>
<td>£9,126,389</td>
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<td>Cost of GP enhanced service per test</td>
<td>£32.00</td>
<td>£32.00</td>
<td>£32.00</td>
<td>£32.00</td>
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<td>Total Annual CCG Saving</td>
<td>£102,545,583</td>
<td>£104,596,495</td>
<td>£106,688,425</td>
<td>£108,822,193</td>
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<td>Cumulative Saving</td>
<td>£102,545,583</td>
<td>£207,142,078</td>
<td>£313,830,503</td>
<td>£422,652,696</td>
<td>£533,651,333</td>
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</table>
References

1. Data on File, Ferring UK Ltd, May 2013
2. HES data, March 2013
3. PBR data, March 2013
15. The NHS Technology Adoption Centre: Faecal Calprotectin Testing in Primary Care. June 2013
16. Data on File, 2013, Ferring UK Ltd
20. Eurostat UK population data HES Online data, March 2013